PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* 01-11-2004

Applicant's or agent's file reference
72294-76325

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE2004/001038	07.07.2004	07.07.2003

International Patent Classification (IPC) or both national classification and IPC
A61K 39/39

Applicant
Isconova AB et al

1. This opinion contains indications relating to the following items:

- [X] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [X] Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [X] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further opinions, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Form PCT/ISA/237 (cover sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SE2004/001038

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SE2004/001038

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	5-8, 13	YES
	Claims	1-4, 9-12, 14	NO
Inventive step (IS)	Claims		YES
	Claims	1-14	NO
Industrial applicability (IA)	Claims	1-14	YES
	Claims		NO

2. Citations and explanations:

The present application relates to the use of fraction A of Quil A together with at least one other adjuvant for the preparation of an adjuvant composition with synergistic effect to enhance the level and quality of immunomodulating activity. It especially relates to the use of fraction A of Quil A together with one or more other adjuvants, where fraction A at a low and well tolerated dose synergistically enhances the immuno-enhancing effect of the co-administered adjuvant, which on its own is too toxic for prophylactic or clinical use.

The following documents (D) are cited in this opinion:

1. (D1) WO 9611711 A1.
2. (D2) Johansson M, Lovgren-Bengtsson K. Iscoms with different quillaja saponin components differ in their immunomodulating activities. *Vaccine*. 1999 Jul 16;17(22):2894-900.
3. (D3) Behboudi S, Morein B, Villacres-Eriksson MC. Quillaja saponin formulations that stimulate proinflammatory cytokines elicit a potent acquired cell-mediated immunity. *Scand J Immunol*. 1999 Oct;50(4):371-7.
4. (D4) Ekstrom J, Hu KF, Bengtsson KL, Morein B. Iscom and iscom-matrix enhance by intranasal route the IgA responses to OVA and rCTB in local and remote mucosal secretions. *Vaccine*. 1999 Jun 4;17(20-21):2690-701.

D1 discloses the use of fraction A of Quil A together with fraction C of Quil A for the preparation of an adjuvant composition with synergistic effect to enhance the level and quality of immunomodulating activity. It is also specifically disclosed that fraction C of Quil A on its own is too toxic for prophylactic or clinical use (see specially page 8, table 1 and the last paragraph).

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

D2 discloses the use of fraction A of Quil A together with fraction C of Quil A for the preparation of an adjuvant composition with synergistic effect to enhance the level and quality of immunomodulating activity (see Iscoprep 703). D2 also suggests the use of fraction A of Quil A together with other adjuvants for the preparation of an adjuvant composition (see specially page 2899, col. 1, lines 13-16).

D3 discloses the use of fraction A of Quil A together with fraction C of Quil A for the preparation of an adjuvant composition with synergistic effect to enhance the level and quality of immunomodulating activity (see specially page 376, col. 2, lines 26-35).

D4 describes the use of iscom particles in combination with, *inter alia*, Cholera toxin (CT). Questions such as the two following are investigated in this article: "Can synergy occur between two adjuvant systems?" "If two adjuvant systems are used, should they be administered in the same particle or not?" (see the discussion).

Novelty:

D1-D3 disclose the use of fraction A of Quil A together with another adjuvant (fraction C of Quil A) for the preparation of an adjuvant composition with synergistic effect to enhance the level and quality of immunomodulating activity. Hence, the invention according to claims 1-4, 9-12 and 14 is already known.

According to the motivation above claims 1-4, 9-12 and 14 lack novelty.

Inventive step:

D1, which is considered to represent the most relevant prior art, discloses the use of fraction A of Quil A together with another adjuvant (fraction C of Quil A) for the preparation of an adjuvant composition with synergistic effect to enhance the level and quality of immunomodulating activity.

The main technical difference in terms of claimed technical features between the invention according to claims 5-8 and 13 and D1, is that in the claimed invention further examples of adjuvants that fraction A of Quil A can be combined with are given (*inter alia* CT or monophosphoryl lipid A).

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of: Box V

The technical effect that this difference achieves is further examples of adjuvant formulations where fraction A of Quil A is combined with another adjuvant to create a synergistic effect and give an adjuvant composition with enhanced immunomodulating activity.

The problem to be solved is, therefore, to create alternative adjuvant compositions, of fraction A of Quil A combined with another adjuvant, with enhanced immunomodulating activity.

A solution to this problem is indicated in documents D1-D3 (D2 and D3, which could be considered in a similar manner as D1, *vide supra*, as the most relevant prior art). In these documents it is already shown that fraction A of Quil A, which has low toxicity and good immunomodulating activity, can be combined with another adjuvant, which has greater activity but has to high toxicity when administered alone (see D1 page 8, table 1 and the last paragraph and D3 page 376, col. 2, lines 26-35). Actual suggestions to combine fraction A of Quil A with other adjuvants are given in D1 and D2 (see D1 page 4, lines 4-9 and D2 page 2899, col. 1, lines 13-16).

Hence, since the advantage of combining a high toxicity adjuvant with fraction A of Quil to create a synergetic effect is know, it is considered obvious for a person skilled in the art to solve the problem of creating alternative adjuvant compositions with a similar synergetic effect. Further, no surprising technical effect has been shown and the application and D1-D3 belong to the same technical field.

A further technical difference in terms of claimed technical features between the invention according to claims 5-8 and 13 and D1, is that the adjuvants in the claimed invention can be administered in separate particles. The technical effect that this difference achieves is not clearly described. It is however already know, inter alia, in D4 that adjuvants can be administered in separate particles. Therefore, this difference also does not constitute a non-obvious technical difference.

Consequently, according to the motivation above, the subject matter claimed in claims 1-14 is considered to lack an inventive step.

WRITTEN OPINION OF THE
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International application No.
PCT/SE2004/001038

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawing or on the question whether the claim are fully supported by the description, are made:

Article 6 PCT requires, among other things, that the claims, which define the matter for which protection is sought, are clear and concise. This has to be interpreted as meaning not only that a claim from a technical point of view must be comprehensible, but that it must define clearly the object of the invention, that is to say indicate all the essential technical features, which are necessary to obtain the desired effect, or differently expressed, which are necessary to solve the technical problem with which the application is concerned without undue experimentation.

Claim 1 refers to "a combination of fraction A of Quil A with another adjuvant to form a composition with synergistic effect including enhancement of immune responses and immunomodulating activity". This functional definition of the composition does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The following functional statement does not enable the skilled person to determine which technical features the defined composition composes. In other words, it is not clearly defined which other adjuvants fraction A of Quil A can be combined with.